Trastuzumab deruxtecan for treating HER2-low metastatic or unresectable breast cancer after chemotherapy (ID3935)

Technology appraisal committee A [5 September 2023]

For **PUBLIC** – contains no ACIC information (PART 1 only)

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Key clinical effectiveness issues

Treatment pathway and positioning of trastuzumab deruxtecan

- Does the treatment pathway reflect NHS clinical practice?
- What impact will the new HER2-low categorisation have on the treatment pathway?
- Where would trastuzumab deruxtecan be used in clinical practice?

DESTINY-Breast04 clinical trial

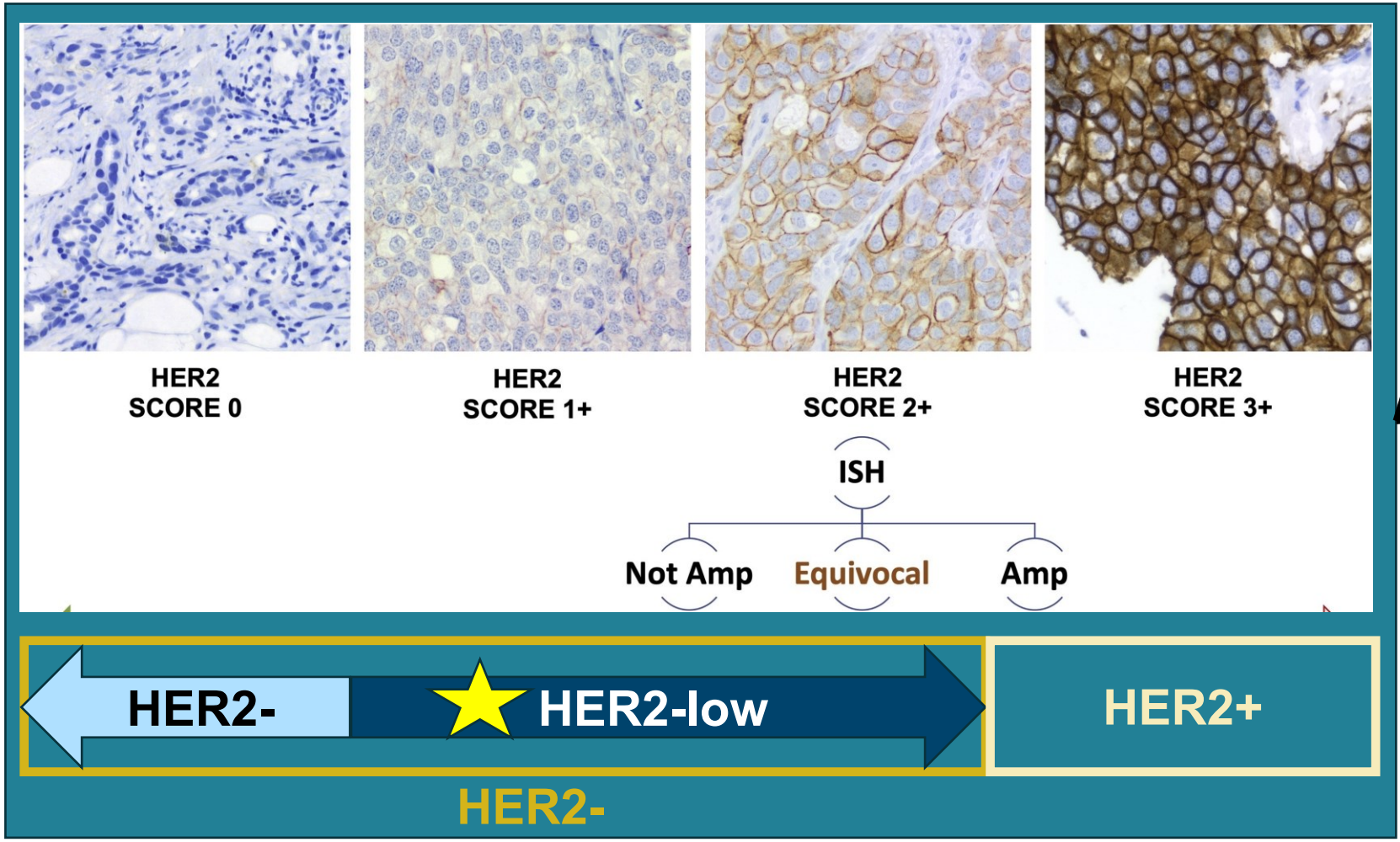
- Is the trial population representative of patients likely to have trastuzumab deruxtecan in the NHS?
- Is the trial comparator arm, treatment of physician choice (TPC) representative of NHS practice? How should TPC be modelled for hormone receptor positive (HR+) and hormone receptor negative (HR-) HER2-low population?

HER2, human epidermal growth factor receptor 2; HR+, hormone receptor positive; HR-, hormone receptor negative; TPC, treatment of physician choice

Background on HER2-low metastatic or unresectable breast cancer

HER2-low is a subset of HER2- in previous classification system

BC: metastatic (spread to other body parts), unresectable (cannot remove by surgery)



HR+ (more common): BC cells have hormone (oestrogen / progesterone) receptors; respond to hormone therapy

HR-: BC cells have no hormone receptors

England 2020:

- ~45k BC cases
- ~6% diagnosed mBC
  - ~35% HER2-low
  - Survival at 1 year (66%) and 5 years (27%)

NICE amp, amplification; BC, breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ISH, in situ hybridisation; mBC, metastatic breast cancer

Trastuzumab deruxtecan (Enhertu)

Marketing authorisation	Treatment of adults with unresectable or metastatic HER2-low breast cancer who have had prior chemotherapy in metastatic setting or had recurrence during or within 6 months of completing adjuvant chemotherapy
Mechanism of action	• HER2-targeted antibody-drug conjugate • Antibody linked to a topoisomerase inhibitor which binds to HER2 on cancer cells. Deruxtecan is released causing DNA damage and apoptotic death to cancer cells
Administration	Intravenous infusion 1x every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity (recommended dosage 5.4mg/kg)
Price	• List price: £1,455 per 100 mg vial • Patient access scheme in place

DNA, deoxyribonucleic acid; HER2, human epidermal growth factor receptor 2

Patient and clinical perspective

Impact of mBC

- Considerable anxiety, fear, uncertainty
- Affects all aspects of life: physical, psychological, social, financial
- No cure: treatments delay progression, extend length and quality of life

People would like

- HER2- (HR+/-): maintain access to available options
- BC redefined: HER2-low BC can access targeted treatments (fewer side effects and better quality of life)
- Flexibility to decide where to use T-DXd in pathway

Trastuzumab deruxtecan

- Unmet need: targeted therapy for new population
- Clinical trial: increases PFS and OS vs standard chemotherapy
- Specific toxicity (interstitial lung disease/pneumonitis): not assessed in real world setting

NICE

BC, breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; mBC, metastatic breast cancer; OS, overall survival; PFS, progression free survival; T-DXd, trastuzumab deruxtecan

Treatment pathway for HER2-negative mBC

T-DXd after chemotherapy

T-DXd?

	HR+	HR-
1L	• Anthracyclines or docetaxel (CG81) • Gemcitabine + paclitaxel (TA116)	• Atezolizumab + nab-paclitaxel (TA639)* • Pembrolizumab + chemotherapy (paclitaxel or nab-paclitaxel; TA801)*
2L	• Vinorelbine or capecitabine (CG81) • **Trastuzumab deruxtecan?**	• Sacituzumab govitecan (TA819)**
3L	• Vinorelbine or capecitabine (CG81)*** • Eribulin (TA423) • **Trastuzumab deruxtecan?**	• Sacituzumab govitecan (TA819)**

Does the treatment pathway reflect NHS clinical practice for HER2-low population? Is this how trastuzumab deruxtecan would be used in practice?

*PD-LI+ disease only; **after ≥2 systemic therapies, 1 for advanced disease; ***whichever was not used at 2nd line; TA639, TA801 and TA819 in triple negative disease; CG, clinical guideline; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; mBC, metastatic breast cancer; TA, technology appraisal; T-DXd, trastuzumab deruxtecan

Clinical effectiveness

NICE National Institute for Health and Care Excellence

DESTINY-Breast04 trial

Phase 3, international, multi-centre (including UK), open-label RCT (Dec 2018 – Jan 2022)

Population

Adults with HER2-low u/mBC after 1 or 2 lines of chemotherapy in (neo)adjuvant (if recurrence occurs within 6 months) or metastatic setting

- **ECOG PS: 0 or 1**

Intervention and comparator

T-DXd; IV every 3 weeks @ 5.4 mg/kg of body weight n=373

Treatment of Physician Choice, TPC (capecitabine, eribulin, gemcitabine, nab-paclitaxel, paclitaxel) n=184

Outcomes

- **Primary endpoint:** PFS (BICR) in HR+
- **Secondary:**
  - PFS (BICR) in FAS
  - OS in HR+ and FAS
  - Safety (AEs)
  - HRQoL (EQ-5D)
  - ORR (BICR) in HR+

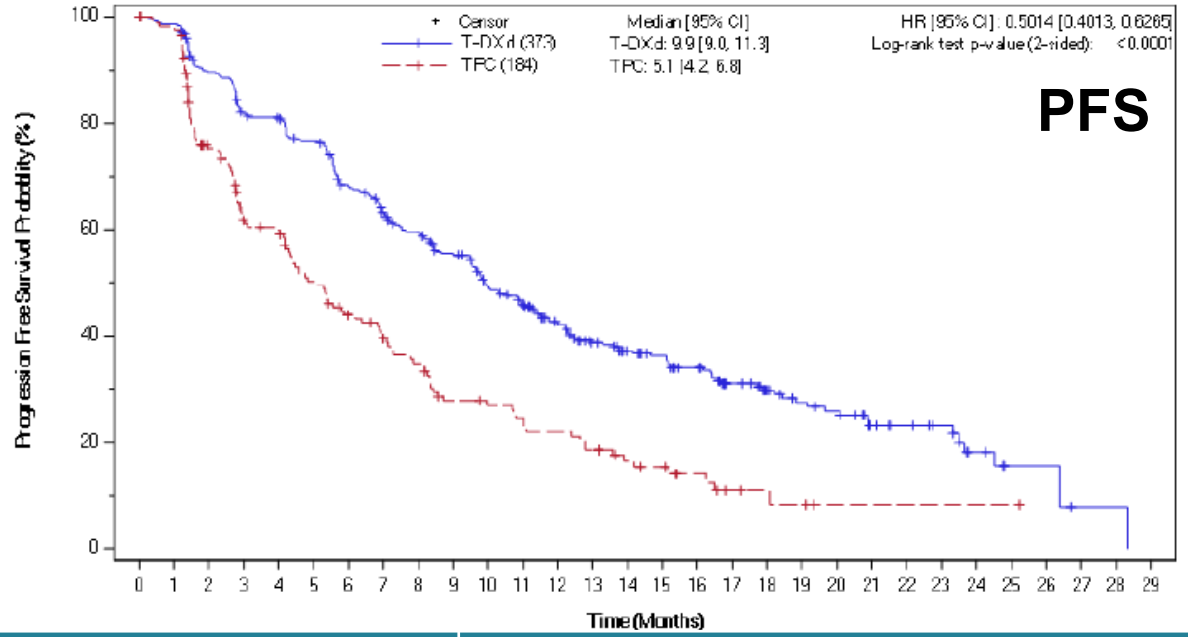
Main baseline characteristics

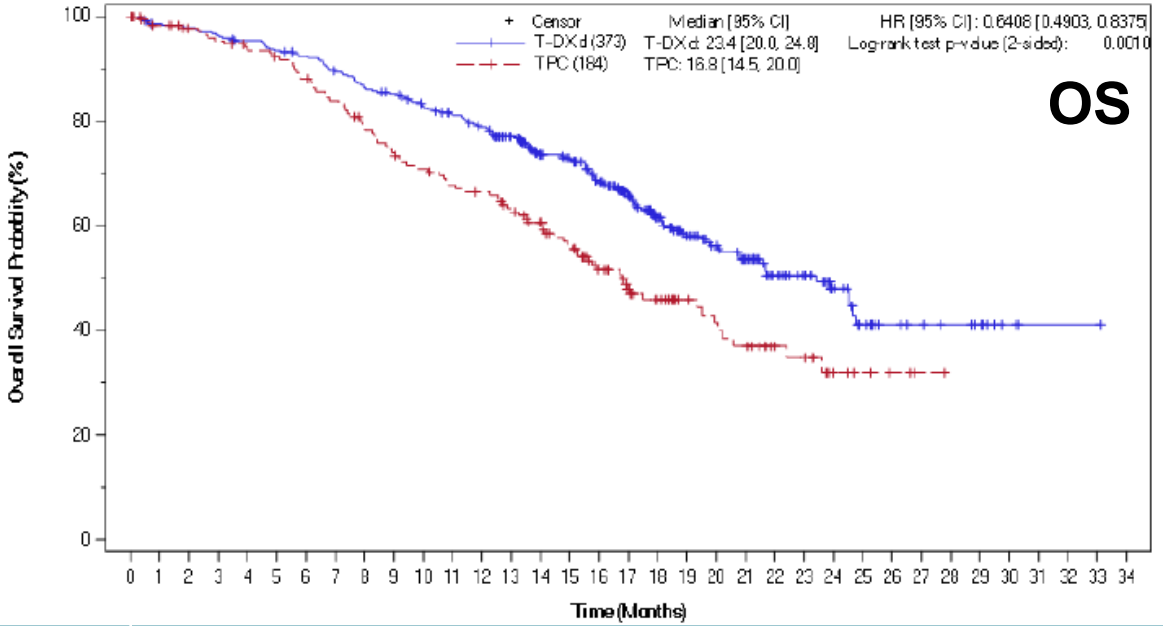
- Mean age: 57 years
- Ethnicity: 48% White, 40% Asian, 2% Black
- In metastatic setting: 58% 1 prior chemotherapy, 41% 2 lines

FAS (full analysis set): 100% randomised (n=557)
HR+: 89% (n=494)
HR-: 11% (n=63)
SAS (safety analysis set): 98% (n=543)

AE, adverse event; BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EQ-5D, EuroQoL-5 dimensions; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; HRQoL, health-related quality of life; IV, intravenous; n, number; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; T-DXd, trastuzumab deruxtecan; u/mBC, unresectable/metastatic breast cancer

DESTINY-Breast04 results: PFS and OS in FAS (HR+ and HR-)





Population	PFS [Median (95% CI)], months		OS [Median (95% CI)], months	
	T-DXd	TPC	T-DXd	TPC
FAS: 373 T-DXd; 184 TPC	10 (9, 11)	5 (4, 7)	23 (20, 25)	17 (15, 20)
	HR: 0.5 (0.4, 0.6), p<0.0001		**HR: 0.6** (0.5, 0.8), p=0.001	
HR+: 331 T-DXd; 163 TPC	10 (10, 12)	5 (4, 7)	24 (21, 25)	18 (15, 22)
	HR: 0.5 (0.4, 0.6), p<0.0001		**HR: 0.6** (0.5, 0.9), p=0.0028	
HR-: 40 T-DXd; 18 TPC	9 (NR)	3 (NR)	18 (NR)	8 (NR)
	HR: 0.5 (0.2, 0.9)		**HR: 0.5** (0.2, 0.95)	

Key issue: Representativeness of DESTINY-Breast04 population

Background

- Trial population may not be representative of people likely to have T-DXd in the NHS
  - Trial: younger, excluded ECOG PS ≥2, many of Asian descent

Company

- Subgroup analysis consistent for Asian (n=223) and White (n=267)
- Real world data: similar median age of people treated with T-DXd

EAG comments

- Company PFS subgroup analysis on ethnicity not consistent
- Company did not provide evidence for ECOG PS 2 (part of indication)
- Characteristics are potential treatment effect modifiers
- Unclear representativeness of NHS patients

Is population in DESTINY representative of patients likely to have T-DXd in the NHS?

ECOG PS, Eastern Cooperative Oncology Group Performance Status; n, number; PFS, progression-free survival; T-DXd, trastuzumab deruxteca

Key issue: Representativeness of TPC (1)

Background

- Trial control arm was TPC (n=184): 51% eribulin, 20% capecitabine, 10% gemcitabine, 10% nab-paclitaxel, 8% paclitaxel*
- EAG noted different to NHS practice: Gemcitabine not used as single agent; anthracyclines and carboplatin used 2L; eribulin recommended 3L, only not 2L; SG used for HR-
- Company assumed all TPC options are similarly effective
- Company did separate cost-minimisation analysis of T-DXd vs SG

Company

- Maintains base case with TPC. Maintains separate cost-minimisation analysis for SG
- Exploratory trial post-hoc analysis: removed 2L eribulin and gemcitabine
  - Adjusted TPC: [redacted]% 3L eribulin, [redacted]% capecitabine, [redacted]% nab-paclitaxel, [redacted]% paclitaxel*
    - Outcomes similar for base case and exploratory analysis

Other considerations (TE clinical expert feedback)

- **HR+:** 2L chemotherapy monotherapy (paclitaxel / epirubicin / capecitabine). 3L eribulin
- **HR-:** 2L SG if prior taxane and adjuvant chemotherapy. 3L eribulin

*proportions do not add up to 100% because of rounding; 2L, 2nd line; 3L, 3rd line; HR, hormone receptor; n, number; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan; TE, technical engagement; TPC, treatment of physician choice

Key issue: Representativeness of TPC (2)

EAG comments

- TPC arm does not represent NHS practice
- Removed gemcitabine and eribulin, redistributed costs 54% capecitabine, 25% nab-paclitaxel, 21% paclitaxel (base case)
- Lack of evidence for anthracyclines, carboplatin and vinorelbine in CS. Cannot assess impact
- For HR-, comparison of T-DXd with SG is uncertain (details in slides 28-29)
- Issues with company exploratory post hoc analysis:
  - Used updated parametric curves to "adjusted TPC" population → EAG cannot assess impact (company did not submit analysis)
  - Smaller sample → reduced generalisability of CE estimates to target population
  - Large effect: 7% decrease in ICER, >10% decrease in total discounted QALYs

What represents standard of care? Is DESTINY's TPC representative of NHS practice? How should TPC be modelled for HR+/HR- HER2-low population?

CE, cost effectiveness; CS, company submission; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ICER, incremental cost-effectiveness ratio; QALY, quality adjusted life years; SG, sacituzumab govitecan; TPC, treatment of physician choice

Cost effectiveness

NICE National Institute for Health and Care Excellence

Key cost effectiveness issues

- OS extrapolation: Which is more plausible? Log-logistic or Weibull?
- PFS extrapolation: Which is more plausible? Log-logistic or generalised gamma?

Utilities

- Which utility values best reflect progression-free state; progressed disease in the short term and long term?
- How long would people having T-DXd continue to benefit after they have progressed? 6 or 12 months?
- TTD extrapolation: How should it be modelled?
- Vial sharing: what proportion should be modelled? 50% or 75%?

Trastuzumab deruxtecan (T-DXd) vs sacituzumab govitecan (SG) for HR-

- Is SG clinically equivalent to T-DXd?
- Is the cost minimisation analysis SG vs T-DXd robust for decision making?

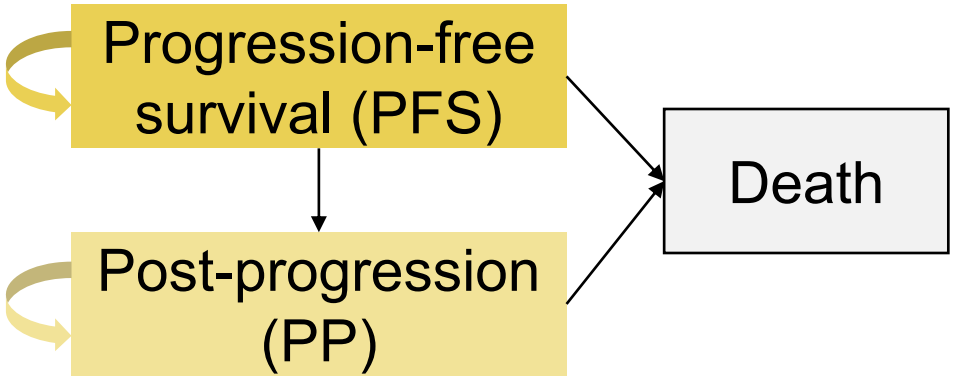
Other

- Are there any benefits not captured in model? Which QALY weighting should be applied?
- Are there any equality issues to consider?

HR, hormone receptor; OS, overall survival; PFS, progression-free survival; QALY, quality adjusted life years; TTD, time to treatment discontinuation

Company's model overview

Model structure



- Technology affects **costs** by its higher cost vs TPC
- Technology affects **QALYs** by increasing length of life and improving QoL
- Assumptions with greatest ICER impact:
  - OS extrapolation
  - PFS extrapolation
  - PF utility modelling
  - Removing eribulin and gemcitabine
  - TTD extrapolation

- Partitioned survival model: 30-year time horizon, 3-week cycle, half cycle correction
- UK NHS and PSS perspective, annual discount rate of 3.5% for costs and QALYs
- T-DXd vs TPC (capecitabine, eribulin, gemcitabine, nab-paclitaxel, paclitaxel)

ICER, incremental cost-effectiveness ratio; OS, overall survival; PSS, personal social services; QALY, quality adjusted life years; QoL, quality of life; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician choice; TTD, time to treatment discontinuation

How company incorporated evidence into model

Input	Assumption and evidence source
Modelled population	• DESTINY FAS: 99.6% female, mean age 57 years, mean weight [redacted]kg, mean BSA [redacted]m^2
Intervention and comparator efficacy	• PFS, OS and TTD: DESTINY FAS data • AEs: Grade ≥3 in ≥5% of patients; ILD of any grade
Utilities	• PF utilities: DESTINY EQ-5D data • PP utilities: Lloyd (2006) algorithm, DESTINY characteristics
Resource use and costs	• Treatment: duration per TTD; RDI from DESTINY by arm • Subsequent treatment: DESTINY by arm • AEs: non-elective short hospital stay; fatigue 1-hour hospital nursing time • Administration: day-case (1st), outpatient (subsequent) • Frequency: 1x IV, 1x/cycle capecitabine, 1x/pack oral • Health state: GP, oncologist, clinical nurse specialist, CT, ECG
All-cause mortality	All-cause mortality for general population (England and Wales)

AE, adverse event; BSA, body surface area; CT, computer tomography; ECG, electrocardiogram; EQ-5D, Euro-QoL-5D; FAS; full analysis set; GP, general practitioner; ILD, interstitial lung disease; IV, intravenous; OS, overall survival; PFS, progression-free survival; PP, post-progression; RDI, relative dose intensity; TTD, time to treatment discontinuation

Summary of key issues: company and EAG preferred assumptions

	Company's original base case	EAG-preferred analysis	Company's updated base case
TPC: remove eribulin and gemcitabine; redistribute %	No	Yes	No
OS extrapolation	Log-logistic	Weibull	Log-logistic
PFS extrapolation	Log-logistic	Generalised gamma	Log-logistic
PF and PP utilities	disagreement – further details on slides 23-25		
Limit PP utility difference	Life-long	6 months	12 months
TTD extrapolation	Generalised gamma	Unknown	Generalised gamma
Vial sharing	75%	50%	75%
SG analysis: include time on SG from ASCENT	No	Yes	No
Additional issues			
TTD extrapolation	EAG: uncertainties about modelling		
Severity modifier	-	-	1.2x is conservative

OS, overall survival; PFS, progression-free survival; PP, post-progression; SG, sacituzumab govitecan; TPC, treatment of physician choice; TTD, time to treatment discontinuation

Key issue: OS extrapolation (1)

Background

- Company used DESTINY KM data to extrapolate OS
  - Company base case: log-logistic (best statistical and visual fit; clinically plausible conservative long-term estimates, similar to trial TPC)
- EAG disagrees with log-logistic (overestimates OS, similar to excluded log-normal)
  - Considers exploration of gamma distribution warranted
  - EAG base case: Weibull (statistical and visual fit; aligns with EAG clinical advisors' views that ≤1% likely alive at 10 years)

Company

- Maintains log-logistic for base case
  - DESTINY OS data mature and robust (key secondary endpoint of OS in FAS met)
  - Unnecessary to explore gamma distribution: company's exploration includes the 6 distributions suggested by DSU TSD 14

EAG comments

- Maintains Weibull for base case
  - Statistical goodness-of-fit scores near identical for log-logistic and Weibull

FAS, full analysis set; KM, Kaplan-Meier; OS, overall survival; TPC, treatment of physician choice

Key issue: OS extrapolation (2)

Observed vs predicted OS; FAS 10 years

Model	Med (mth)	% alive at Year					
		1	1.5	2	3	5	10
DB04	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Model	Med (mth)	% alive at Year					
		1	1.5	2	3	5	10
DB04	[redacted]	[redacted]	[redacted]	[redacted]	-	-	-
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Which curve provides most clinically plausible OS extrapolation? Log-logistic or Weibull?

Key issue: PFS extrapolation (1)

Background

- Company used DESTINY KM data to extrapolate PFS (endpoint met in trial)
  - Company base case: log-logistic (statistical criteria, visual fit, consistent with OS extrapolation; T-DXd and TPC generalised gamma curves cross at ~5 years)
- EAG disagrees with log-logistic (overestimates tail of T-DXd)
  - EAG base case: generalised gamma (KM curves about to cross at end of trial)
  - Scenario: cap on fitted curves at crossing point, PFS same for both arms

Company

- EAG scenario: implausible same PFS for T-DXd and TPC at 5 years
- Maintains log-logistic for base case

EAG comments

- Median predicted PFS from generalised gamma and log-logistic identical
- Company did not use suggested approach (mature KM data, extrapolations beyond KM)
- Company's extrapolation using spline models may be most appropriate (not explored)
- Maintains generalised gamma for base case

KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician choice

Key issue: PFS extrapolation (2)

Observed vs predicted PFS; FAS 10 years

[redacted]

Timepoint (months)	T-DXd			TPC		
	DB-04 observed	Log-logistic	Generalised gamma	DB-04 observed	Log-logistic	Generalised gamma
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Which curve provides most clinically plausible PFS extrapolation? Log-logistic or generalised gamma?

Key issue: Progression-free utilities

Background

- Company base case: PF utilities from DESTINY EQ-5D-5L data by arm using generalised linear mixed model (GLMM)
- EAG: utilities lacked face validity (high [redacted] T-DXd, [redacted] TPC vs 0.84 general population for severity modifier and in appraisal TA862, 0.835 T-DXd and 0.801 comparator)
  - EAG base case: used trial summary mean utilities (greater face validity)

Company

- Maintain base case using GLMM (more robust as less biased by extreme outliers and account for effects of covariates and intra-subject correlation; similar to TA862, HER2+ after ≥1 anti-HER2 in u/mBC)
- Scenarios: 1) median PF utilities from DESTINY; 2) PF utilities from linear mixed model

EAG comments

- Company scenarios' estimates closer to EAG's (lower than estimates using GLMM)
- Acknowledges limitations of using summary mean utilities
  - EAG revised base case: company's linear mixed effect model scenario

EQ-5D, EuroQoL-5 dimensions; HER2, human epidermal growth factor receptor 2; PF, progression free; TA, technology appraisal; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician choice; u/mBC, unresectable/metastatic breast cancer

Key issue: Post-progression utilities

Background

- Company used Lloyd algorithm and trial inputs (age, treatment response, progression), not trial EQ-5D (utilities high compared to previous appraisals)
  - Assumed T-DXd have higher utilities than TPC, which persisted for lifetime
- EAG: Lloyd inconsistent with NICE reference case
  - Disagrees with pre-progression rates (52% T-Dxd vs 16% TPC) to estimate PP utilities
  - TA819: PP difference in utilities for 6 months after progression only
  - EAG base case: applied Lloyd's progressed disease utility decrement (0.272) to trial PF utilities to estimate treatment-specific PP utilities. PP difference limited to 6 months after progression (then everyone adopt TPC utility)

Company

- Maintain base case, but restricts T-DXd PP benefit to 12 months, and then TPC utility for both arms

EAG comments

- Company estimates larger difference in arms post- than pre-progression in trial
- Company did not apply Lloyd algorithm appropriately; used different ages in arms
- EAG updated base case: decrement using trial average age to both arms (0.243 vs 0.272)

EQ-5D, EuroQoL-5 dimensions; PF, progression-free; PP, post-progression; TA, technology appraisal; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician choice

Key issue: Utilities

Base case	Source for utilities	Progression-free (PF)		Post-progression (PP)		Duration of PP benefit	PP – long-term	
		T-DXd	TPC	T-DXd	TPC		T-DXd	TPC
Company post-TE	PF: GLMM PP: Lloyd	[redacted]	[redacted]	0.6101	0.5655	12 months	0.5655	0.5655
EAG post-TE	PF: linear mixed model PD=PFS-0.243; Lloyd – age	[redacted]	[redacted]	[redacted]	[redacted]	6 months	[redacted]	[redacted]

Which utility values best reflect the progression-free state?
Which utility values best reflect the post-progression state in the short term?
How long would people on T-DXd continue to benefit after they have progressed? 6 or 12 months?
Which utility values best reflect progressed disease in the long term?

T-DXd, trastuzumab deruxtecan; TE, technical engagement; TPC, treatment of physician choice

Key issue: TTD extrapolation

Background

- Company base case: used generalised gamma to extrapolate TTD data
- EAG requested analysis: KM data followed by extrapolation
  - Scenarios: restricted mean treatment duration approach used as lower limit for treatment duration (favours company) and log-logistic TTD extrapolation used as upper limit

Company

- Maintains base case but acknowledges EAG scenarios
  - Scenarios provide limited additional value, minimal impact on ICER. Using parametric curves allow inclusion of time-on-treatment in PSA. EAG scenario using restricted mean treatment duration approach decreased ICER

EAG comments

- Company did not submit requested analyses, nor showed evidence of minimal impact on ICER. EAG scenarios had large effect on ICERs
- Consider issue unresolved

How should TTD extrapolation be modelled?

ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; PSA, probabilistic sensitivity analysis; TTD, time to treatment discontinuation

Key issue: Vial sharing

Background

- Company assumes vial sharing leads to no wastage in 75% of T-DXd and TPC IV
- TA862: 50%
- EAG base case: 50%

Company

- TA862: CDF clinical lead suggested vial sharing occur in ≥50% cases
  - HER2+ is smaller subset of mBC than HER2-low → HER2-low increased opportunity for vial sharing
- EAG base case applying 50% vial sharing may be an underestimate

EAG comments

- Company provides no evidence to support 75% assumption.
- Maintains base case of 50% to align with TA862

What percentage should be assumed for vial sharing? 50% or 75%?

CDF, Cancer Drug Fund; HER2, human epidermal growth factor receptor 2; TA, technology appraisal; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician choice

Key issue: Absence of sacituzumab govitecan from TPC (1)

Background

- Company: no comparative data for T-DXd and SG (ITC not feasible; naïve, unadjusted comparison: HRs for PFS and OS similar for T-DXd vs TPC and SG vs TPC)
- Cost-minimisation analysis: equivalent clinical effectiveness (PFS, OS, AEs, TTD)
- EAG: Company did not provide analysis to assess if T-DXd, SG or TPC is most cost-effective option in HR- (generally worse outcomes)
  - Effectiveness of SG vs standard care in HER2-low is unknown
  - EAG base case: used average weight for HR- from DESTINY, RDI estimates and time-on-treatment for SG from TA819

Company

- No RWE for T-DXd vs SG in HER2-low
- Agrees with EAG base case, **except** using SG time-on-treatment data from TA819
  - Used Grade ≥3 TEAE rates from DESTINY for T-DXd and ASCENT for SG

EAG comments

- Caution interpreting naïve unadjusted comparison (different populations)
- Company use of TEAEs insufficient to estimate costs related to SG
- EAG updated base case: as before, plus SG-specific TEAEs

AE, adverse event; HR, hazard ratio; HER2, human epidermal growth factor receptor 2; ITC, indirect treatment comparison; OS, overall survival; PFS, progression-free survival; RDI, relative dose intensity; RWE, real world evidence; SG, sacituzumab govitecan; TA, technology appraisal; T-DXd, trastuzumab deruxtecan; TEAE, treatment emergent AE; TPC, treatment of physician choice; TTD, time to treatment discontinuation

Key issue: Absence of sacituzumab govitecan from TPC (2)

Other considerations (comments from commentator)

- T-DXd and SG not clinically equivalent: different safety profiles and populations in trials

ASCENT: open-label, phase 3 RCT

- Population: 529 unresectable, locally advanced or metastatic triple-negative BC refractory or relapsed after ≥2 chemotherapies (≥1 for locally advanced / metastatic setting)
- Comparator: TPC – capecitabine, eribulin, gemcitabine, vinorelbine

Trial	Analysis	Outcome	Median, months	Difference, months	HR (95% CI)
DB-04	T-DXd vs TPC	PFS	T-DXd: 9 vs TPC: 3	6	0.5 (0.2, 0.9)
		OS	T-DXd: 18 vs TPC: 8	10	0.5 (0.2, 0.95)
ASCENT	SG vs TPC	PFS	SG: 6 vs TPC: 3	3	0.4 (0.3, 0.7)
		OS	SG: 14 vs TPC: 9	5	0.4 (0.3, 0.7)

EAG comments

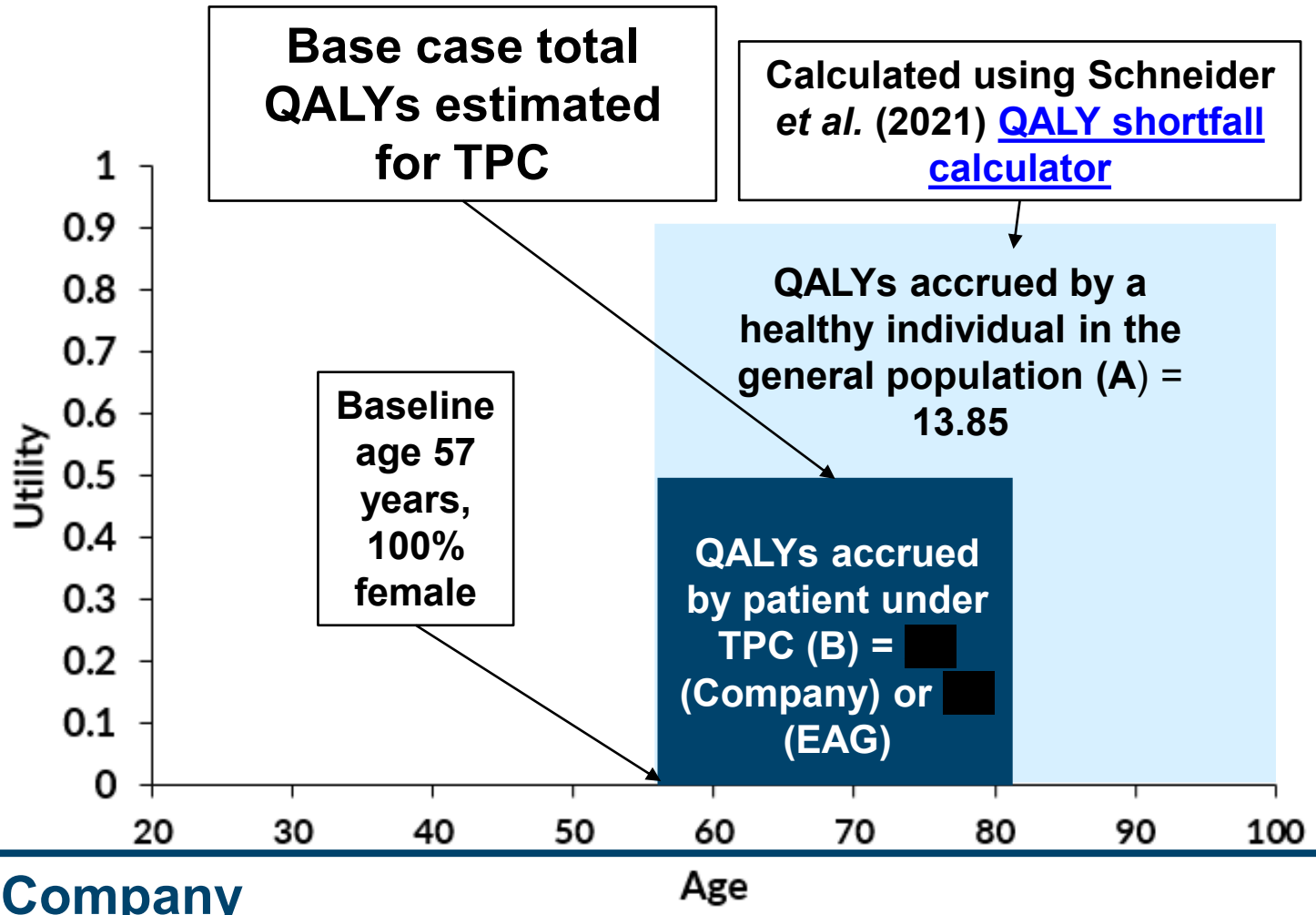
- DESTINY 2L vs ASCENT 3L (more difficult to treat; PFS utility lower) → affects relative efficacy

Is SG clinically equivalent to T-DXd?
Is the cost minimisation analysis SG vs T-DXd robust for decision making?

NICE

2L, 2nd line; 3L, 3rd line; BC, breast cancer; DB-04, Bestiny-Breast04; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician choice

QALY weighting for severity



QALY shortfall	Company	EAG
Absolute	[redacted]	[redacted]
Proportional	[redacted]	[redacted]

QALY weight	QALY shortfall	
	Absolute	Proportional
1	<12	<0.85
1.2	12-18	0.85 to 0.95
1.7	≥18	≥0.95

The weight of 1.2 was applied

Company

- 1.2 weight underestimates disease severity, high unmet need, innovation, clinical value; benefits not captured in QALY calculation e.g. employment

Any benefits not captured in model? Which weighting should be applied?

Summary of company and EAG base case assumptions

	Company	EAG
TPC: remove eribulin and gemcitabine; redistribute %	No	Yes
OS extrapolation	Log-logistic	Weibull
PFS extrapolation	Log-logistic	Generalised gamma
PF utilities	GLMM	Linear mixed effects model
PP utilities	Lloyd	PD = PFS – 0.243; Lloyd (age)
Limit PP utility difference	12 months	6 months
TTD extrapolation	Generalised gamma	Generalised gamma (high uncertainty; unexplored)
Vial sharing	75%	50%
SG analysis only: include time on SG from ASCENT	No	Yes

NICE

GLMM, generalised linear mixed model; OS, overall survival; PD, progressed disease; PFS, progression-free survival; PP, post-progression; SG, sacituzumab govitecan; TPC, treatment of physician choice; TTD, time to treatment discontinuation

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

Impact of key issues on ICER

All ICERs were above £36,000 using QALY weight of 1.2

All scenarios increased ICERs further

Scenario	Impact on ICER compared to company base case
TPC: remove eribulin and gemcitabine; redistribute %	Medium
OS extrapolation	Large
PFS extrapolation	Medium
PF utilities	Medium
PP utilities and limit PP utility difference	Small
Vial sharing	Small
TTD extrapolation	Unknown (potentially large)
CMA T-DXd vs SG: time on treatment for SG from ASCENT	Large

CMA, cost-minimisation analysis; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; PP, post-progression; SG, sacituzumab govitecan; TPC, treatment of physician choice; TTD, time to treatment discontinuation

Equality considerations

- Concern that absolute shortfall in severity modifier calculation discriminates against protected characteristic of age and proportional shortfall does not adequately reduce this impact

Are there any equality issues to consider?

NICE National Institute for Health and Care Excellence

Thank you